



Invariant NKT cells drive hepatic cytokinic microenvironment favoring efficient granuloma formation and early control of *Leishmania donovani* infection

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Résumé en anglais

The development of inflammatory granulomas around infected Kupffer cells is necessary for hepatic parasite clearance during visceral leishmaniasis. Invariant NKT (iNKT) cells are predominant T cells in the mouse liver and can synthesize large quantities of IL-4 and IFN- γ , two cytokines involved in granuloma formation. This study analyzed the role of iNKT cells in the hepatic immune response during *Leishmania donovani* infection, using a murine model of wild-type (WT) and iNKT cell-deficient (J α 18-/-) C57BL/6 mice sacrificed 15, 30 or 60 days post-infection. We recorded hepatic parasite loads, cytokine expression, and analyzed granulomatous response by immunohistochemistry and hepatic immune cell infiltration by flow cytometry. Whereas WT animals rapidly controlled the infection and developed an inflammatory response associated with a massive influx of iNKT cells observed by flow cytometry, J α 18-/- mice had significantly higher parasitic loads on all time points. This lack of control of parasite burden was associated with a delay in granuloma maturation (28.1% of large granulomas at day 60 versus 50.7% in WT). Cytokine transcriptome analysis showed that mRNA of 90/101 genes encoding chemokines, cytokines and their receptors, was underexpressed in J α 18-/- mice. Detection of IL-4 and TNF- α by ELISA in liver extracts was also significantly lower in J α 18-/- mice. Consistent with flow cytometry analysis, cytokinome profile in WT mice showed a bias of expression towards T cell-chemoattractant chemokines on D15, and displayed a switch towards expression of granulocytes and/or monocytes - chemoattractant chemokines on D60. In J α 18-/- mice, the significantly lower expression of CXCL5, MIP-2 and CCL2 mRNA was correlated with a defect in myeloperoxidase positive-cell attraction observed by immunohistochemistry and with a lower granulocyte and monocyte infiltration in the liver, as shown by flow cytometry. These data indicate that iNKT cells play a role in early and sustained pro-inflammatory cytokine response warranting efficient organization of hepatic granulomas and parasite clearance.

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